PROPOSAL FOR TOPIC APPROVAL TO BE SUBMITTED TO THE UNIVERSITY OF MUMBAI FOR THE DEGREE OF

Ph.D.(Pharmaceutical Technology) IN THE SUBJECT OF PHARMACEUTICS

Title of the Topic	:	Lipid Based Drug Delivery System for Cancer Treatment
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Title: Lipid Based Drug Delivery System For Cancer Treatment

Review of literature:

Drug molecules have to cross BBB so as to reach the brain. Reason for poor bioavailability of drug in brain is it either fails to cross the BBB due to poor penetration or due to the efflux mechanism of the brain. To overcome these problems, various colloidal delivery systems have been studied by different researchers such as liposomes, microspheres, lipid microspheres, niosomes, polymeric nanoparticles and solid lipid nanoparticles (SLNs) [1-8]

Chen et al have worked on polymeric nanoparticles as suitable delivery systems for brain. The authors proposed various mechanisms for nanoparticle mediated drug uptake by the brain, including: i) the enhanced retention in the brain--blood capillaries, with an adsorption on to the capillary walls, resulting in a high concentration gradient across the BBB; ii) by opening of tight junctions due to the presence of nanoparticles and iii) by transcytosis of nanoparticles through the endothelium. [9]

Polysorbate coated polymeric nanoparticle showed enhanced drug delivery to brain, at the same time they suffered from various problems like residual contamination from the production process, for example by organic solvents, polymerization initiators, large polymer aggregates, toxic monomers and toxic degradation products. [10,11]

In the late 1990s, Yang et al [12] and Zara et al [13] have anticipated the use of SLN for targeting drugs to brain.

Neves AR et al created a new system to enter the brain by functionalizing solid lipid nanoparticles with apolipoprotein E, aiming to enhance their binding to low-density lipoprotein receptors on the blood-brain barrier endothelial cells. In this study in-vitro cytotoxic effects were evaluated by MTT and LDH assays in the human cerebral microvascular endothelial cells (hCMEC/D3) cell line, a human blood-brain barrier model. [14]

Mona et al prepared olanzapine loaded self-nanoemulsifying drug delivery systems (SNEDDS) with enhanced self-emulsification properties. The results of their study led to the conclusion that olanzapine- loaded SNEDDS with satisfactory physical stability can be prepared using the proper oil phase, surfactant and cosurfactant at adequate proportions. [15]

Bahadur et al. developed buffered nanoemulsion of ziprasidone hydrochloride (fifth generation antipshychotic) and evaluated its potential for efficacious nose to brain delivery drug delivery in animal models. [16]

Indu et al. developed lipid nanoparticles for evaluation of targeting effect of lipid nanoparticles of drug on glioma cell lines (U-87 MG). [17]

Dan et al. investigated binding affinity of iron oxide nanoparticles by using hCMEC/D3 cell lines. [18]

Ziwi et al achieved brain targeting and studied toxicity of odorranalectin-conjugated nanoparticles by intranasal administration. [19]

Rationale and hypothesis

The blood–brain barrier (BBB) is a highly regulated and efficient barrier that provides a sanctuary to the brain. It is designed to regulate brain homeostasis and to permit selective transport of molecules that are essential for brain function. Unfortunately, drug transport to the brain is hampered by this almost impermeable, highly selective and well-coordinated barrier. It is estimated that more than 98% of the new discovered central nervous system (CNS) potential drugs does not cross the BBB, failing to achieve therapeutic concentration within the brain parenchyma. There are challenges and opportunities associated with the BBB for brain drug delivery. The challenge of delivering an effective therapy to the brain is formidable; solutions will likely involve concerted multidisciplinary approaches that take into account BBB biology as well as the unique features associated with the pathological condition to be treated.

Nanocarriers are an emerging class of drug delivery systems that can be easily tailored to deliver drugs to various parts of the body, including the brain. In the past decade, it has been attracting increasing attention for its use in transport of drug across the BBB due to the rapid increase in understanding of receptors and the fast development in polymer chemistry and nanotechnology. Nanocarriers are unique because of their size and easily tailored structures due to the material used. They can behave like macromolecules in certain circumstances, but they can carry much more drug payload and are capable of controlling drug release. They can carry a range of drugs and their surface properties can be modified. These properties make nanocarriers an attractive alternative for transporting drug across the BBB. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, new frontiers have opened for improving drug delivery. Lipid based nanocarriers have been investigated for delivery of various drugs used in the treatment of brain diseases. A very critical and important requirement for nanoparticulate brain delivery is that the employed nanoparticles should be biocompatible and, moreover, rapidly biodegradable. Meeting requirements such as low cytotoxicity, abundant surface functional groups, high drug binding capacity and significant uptake into the targeted cells, lipid-based nanocarriers represent promising candidates for efficient drug delivery to the brain.

Majority of the drugs available for treatment of brain diseases and disorder have limitation of low bioavailability because of low solubility and first pass metabolism. Lipid-based nanocarriers have potential to carry such drugs and it can become a promising drug delivery system for brain.

In proposed project, lipid based nanocarriers as brain drug delivery system will be developed which can overcome current shortcomings in terms of efficacy. Proposed lipid based nanocarriers can combine the advantages of polymeric nanoparticles, fat emulsions and liposomes while simultaneously avoiding their disadvantages. Lipid based nanocarriers are not taken up readily by the cells of the reticulo endothelial system and thus bypass liver and spleen filtration. Proposed lipid based nanocarriers can be stable over desired time period, very important aspect with respect to the other colloidal carrier systems. Formulated lipid based nanocarriers can have high drug loading efficiency as compared to polymeric nanoparticles. It can be scaled up by using larger version of high-pressure homogenizer. As the process avoids use of organic solvents, it will be green processing with no impact on environment in terms of pollutant or additional energy requirement for solvent removal.

Plan of work:

- **Literature Survey:**

  Thorough literature survey about brain drug delivery will be done and suitable drug candidate will be selected. Literature Survey for analytical method will be done. The details regarding processes used for preparation of nanoformulation will be collected. The information about components used in lipid-based nanoformulation will be compiled.

- **Analytical Method Development:**

  For the routine analysis of drug, suitable analytical method like UV and HPLC will be developed. The method will be validated for specificity, linearity, precision, accuracy, system suitability, LOD, LOQ and robustness.

- **Preliminary Screening:**
  The feasibility of selected drug for proposed system will be checked. Pre-formulation studies such as solubility of drug in chosen components will be carried out for their selection. Drug-excipient compatibility studies will be conducted.

- **Development and evaluation of drug loaded SLN**:

  Lipoidal drug delivery system are composed of physiological and biodegradable lipids dispersed in water and stabilized by suitable surfactant system. The choice of lipid matrix and various processing parameters play a critical role in particle size of carriers. Nanocarrier will be prepared by suitable preparation technique. The type of lipid, concentration of other excipients will be optimized by factorial design technique.

- **Characterization of nanocarriers:**
  Characterization of lipid nanocarriers will be done for investigating properties of carrier by mean particle size, particle size distribution, total drug content, in-vitro drug release, surface morphology, etc.

- **Stability studies:**
  The stability studies of developed nanocarriers will be carried out as per ICH guidelines. Long term $25^0C \pm 2^0C/60\% \pm 5\%RH$, intermediate $30^0C \pm 2^0C/60\% \pm 5\%RH$ and $40^0C \pm 2^0C/75\% \pm 5\%RH$. In addition to above conditions, nanocarriers stability will be also evaluated at refrigeration conditions for 6-12 months. The samples at different storage conditions will be withdrawn periodically and analysed for physical and chemical stability.

- **In-vivo studies:**
  For conducting in-vivo studies permission will be obtained from Institutional Animal Ethics Committee (IEAC). Bioanalytical method for determination of drug in plasma will be developed. Pharmacokinetic and tissue distribution studies of developed nanocarriers will be carried out on animal models.

- **Evaluation of cytotoxicity of developed formulation:**

The cytotoxicity of developed formulation will be determined by suitable method such as MTT assay.

Expected Results/Outcomes

The proposed lipid based nanocarrier drug delivery system for brain will provide more practical evidence regarding feasibility of such system and help in boosting research in the nanotechnology for brain drug delivery.

It will create proof of concept that optimized product is more effective than conventional therapy. The society will be benefited due to availability of more effective treatment for brain diseases. Formulation development studies will confirm use of various excipients in nano formulations, processing parameters and equipment. The project will generate cost effective preparation techniques, amenable to scale up. Characterization of nanoformulation will produce information about relationship between properties of nanoparticles and their functions. Cell line studies will confirm absence of toxicity of the developed formulation. Analytical method used for developed formulation, can be extended for utilization for other such products.

Stability studies will give information about effect of various storage conditions on formulation. Research work can be published in peer reviewed journal as well as can be presented in international conferences. The research work can be patented.

The methodology utilized will also confirm viability of scale-up of product and further commercial utilization. Being green process, chances of acceptance from regulatory authorities are respectable.

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